Remarks

Applicant has carefully studied the non-final Office Action, mailed December 7, 2009 (hereinafter "the Action"). Applicant believes these explanatory remarks are fully responsive to the Action. Accordingly, this important patent application is now in condition for allowance.

Status of the Claims

Claims 19, 23, 26, and 27 were pending and under consideration. No amendments have been made. No claims have been added or canceled. Therefore claims 19, 23, 26 and 27 are presented for consideration.

Claim Rejections - 35 U.S.C. §103(a)

Claims 19, 23, 26 and 27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Thiesing et al. (Blood, 2002) (hereinafter "Thiesing") over Virginia Commonwealth University (WO 02/22133 A1) (hereinafter "VCU"). Applicant respectfully traverses these rejections on the basis that the cited combination fails to teach each and every limitation of the claims; there is no motivation to combine the references; and unexpected results.

Claim 19

Claim 19 discloses a method for inducing apoptosis in imatinib mesylate refractory cancer cells, comprising contacting the living cells with a imatinib mesylate and suberoylanilide hydroxamic acid wherein the living cells are selected from the group consisting of chronic myelogenous leukemia cells and acute lymphoblastic leukemia cells.

The Office cites Theising as teaching that STI571 (imatinib mesylate) has shown significant activity in all phases of CML as well as Philadelphia chromosome positive acute leukemias (ALL). (page 3 of the Action) An express limitation of claim 19 is inducing apoptosis in imatinib mesylate refractory cells. Theising fails to teach this limitation. The Office further

states on page 4 of the Action that Theising teaches that resistance would develop with long-term administration of STI571 and suggest the combination of STI571 with other agents to either prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone. However, the statement that cells can *possibly* become resistant to STI571 is not equivalent to the express limitation in claim 19 of inducing apoptosis in imatinib mesylate refractory cells. Similarly, VCU does not teach the administration of agents to imatinib mesylate refractory cells. As such, the cited combination fails to teach the express limitation of claim 19 of inducing apoptosis in imatinib mesylate refractory cells and thus cannot be said to obviate.

The Office goes on to state that in both ALL and CML, Theising teaches that STI571 should be supplemented with another agent known to treat leukemia, however the agents tested in Theising do not include a histone deacetylase inhibitor. The use of a histone deacetylase inhibitor is not mentioned in the entirety of Theising. Furthermore, it was found that the administration of different agents in conjunction with STI571 had differing results. Theising found that out of four agents tested: two agents (IFN and DNR) exhibited an additive effect when combined with STI571; one agent (Ara-C) exhibited a synergistic effect when combined with STI571; and one agent (HU) exhibited an antagonistic effect when administered with STI571. As shown by the differing results as a result of the combination of STI571 with different agents, it cannot be predicted that the administration of STI571 with a histone deacetylase inhibitor will give synergistic or additive results.

The Office notes that Theising fails to teach supplementing STI571 with suberoylanilide hydroxamic acid. The Office offers VCU to overcome this deficiency. The Office states on page 4 of the Action that VCU discloses the co-administration of *cyclin-dependent kinase inhibitors* with cellular differentiation agents to promote apoptosis in cancer cells. The Office states on page 5 of the Action that Theising teaches that STI571 should be supplemented with another agent known to treat leukemia and that VCU teaches the combination of histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) with cyclin dependent kinases. The Office notes on page 5 that VCU fails to teach the combination of SAHA with a tyrosine kinase inhibitor, imatinib mesylate. The Office further states that it would have been obvious to employ the two agents since both references teach treatment of resistant leukemia. Prior to Applicant's administration of SAHA and imatinib mesylate together, it was not known if

the drugs had a synergistic effect hence there was no reason to combine them. Neither Theising nor VCU discuss the use of SAHA to make imatinib mesylate refractory cells more susceptible to the effects of imatinib mesylate. Furthermore, as stated above, the results of Theising indicate that different agents can have differing effects (synergistic, additive or antagonistic) when administered in combination with STI571 thus one of ordinary skill in the art would not have a reasonable success at obtaining predictable results.

MPEP §2143.02 states that in order to support a claim of obviousness all claim elements must be known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded no more than predictable results to one of ordinary skill in the art.

The Office states on page 6 of the Action that one of ordinary skill in the art could have combined SAHA and imatinib mesylate as claimed for the treatment of leukemia and in combination each element would have performed the same function as it did separately and the results would have been predictable. Applicant respectfully asserts that due to the differences in the underlying mechanisms of the agents; the differing cell types administered to that one of ordinary skill in the art would not achieve predictable results; and the differing results obtained by Theising indicating that combining different chemotherapeutic agents with imatinib mesylate gave a range of results from synergistic to antagonistic.

As stated by the Office on page 4 of the Action, Theising does not teach supplementing STI571 with suberoylanilide hydroxamic acid (SAHA) and uses VCU to overcome this deficiency. VCU teaches the administration of cyclin dependent kinase inhibitors with cellular differentiation agents to promote apoptosis in cancer cells. Claim 19 expressly discloses the administration of imatinib mesylate and SAHA. Imatinib mesylate is a *tyrosine kinase inhibitor* which by itself causes apoptosis. The *cyclin-dependent kinase inhibitors* disclosed in VCU, by contrast, oppose apoptosis. (page 3, lines 16-17) Cyclin-dependent kinase inhibitors block cell cycle progression. (page 4, lines 5-8) In contrast, tyrosine kinase inhibitors inhibit the action of protein kinases particularly the phophorylation of tyrosine. Particularly, imatinib mesylate binds to Bcr-Abl receptors blocking ATP. Given the difference in underlying mechanisms between the cyclin-

dependent kinase inhibitors and the tyrosine kinase inhibitors, it cannot be said to the concurrent administration with SAHA would yield predictable results.

Furthermore, the cells examined in VCU were not imatinib mesylate refractory cells. The cells in VCU were not CML or ALL cells. Theising found that differing cell types had differing responses to the administration of STI517 and various other agents for treating leukemia. One would not have a reasonable expectation of success in combining imatinib mesylate as done in Theising with SAHA as disclosed in VCU. Given that the cells that were used in VCU were not the same as the cells used in Theising, the results of the cited combination would be unpredictable and there is no motivation to combine the references.

As stated *supra*, Theising obtained differing results when combining different chemotherapeutic agents with STI571. Theising found that out of four agents tested: two agents (IFN and DNR) exhibited an additive effect when combined with STI571; one agent (Ara-C) exhibited a synergistic effect when combined with STI571; and one agent (HU) exhibited an antagonistic effect when administered with STI571. As shown by the differing results as a result of the combination of STI571 with different agents, it cannot be predicted that the administration of STI571 with a histone deacetylase inhibitor will give synergistic or additive results. Given these differences in results depending on the agent used, the results of the cited combination would be unpredictable and thus the cited combination cannot be said to obviate.

Claim 23

Claim 23 depends from claim 19 and further recites the limitation that the cells are *exposed to* the imatinib mesylate and the suberoylanilide hydroxamic acid for about 48 hours. The Office states on page 6 of the Action that VCU teaches that the combination of a cyclin-dependent kinase inhibitor and a histone deacetylase inhibitor are co-administered within the time range of 24-72 hours. However, this passage cited by the Office refers to the time window of when the agents can be added, thus the combination of agents are not necessarily in contact with the cells for 48 hours. As such, the cited combination fails to teach each and every limitation of the claims and cannot be said to obviate.

Claim 26

Claim 26 depends from claim 19 and further recites the limitation that the cancer cells are chronic myelogenous leukemia cells that are either accelerated-phase or blast crisis phase. The cited combination does not teach the administration of imitinib mesylate and suberoylanilide hydroxamic acid together to induce apoptosis in *chronic myelogenous leukemia cells* that are in *accelerated-phase or blast crisis phase*. As stated in the original specification at paragraph [0013] treatment with imitinib mesylate alone has been successful with cells in the chronic phase but the accelerated and blast crisis phases prove to be highly resistant to imatinib mesylate. Theising expressly states on page 3199 that the results of the study are applicable to **chronic phase** patients whose current treatment regimens include low-dose, continuous exposure to agents such as IFN and Ara-C. VCU does not disclose the use of the combination of agents on accelerated and blast crisis cells at all. The cancers treated in VCU do not include accelerated or blast crisis CML cells. Neither of the references, nor their combination, teach the administration of either drug to chronic myelogenous leukemia cells in accelerated or blast crisis phase. Given that the cited combination of references fails to teach each and every limitation of the claims, the cited combination cannot be said to obviate.

Claim 27

Claim 27 recites the limitation that the cancer cells are acute lymphoblastic leukemia cells that are either accelerated-phase or blast crisis phase. The cited combination does not teach the administration of imatinib mesylate and suberoylanilide hydroxamic acid together to induce apoptosis in *acute lymphoblastic leukemia cells* that are in *accelerated-phase or blast crisis phase*. Theising expressly states on page 3199 that the results of the study are applicable to **chronic phase** patients whose current treatment regimens include low-dose, continuous exposure to agents such as IFN and Ara-C. No studies were conducted on acute lymphoblastic leukemia cells that are in accelerated-phase or blast crisis phase. Similarly, VCU fails to disclose the administration of a combination of agents to acute lymphoblastic leukemia cells in accelerated or blast crisis phases. Neither of the references, nor their combination, teach the administration of either drug to acute lymphoblastic leukemia cells in accelerated or blast crisis phase. Given that the cited combination of references fails to teach each and every limitation of the claims, the cited combination cannot be said to obviate.

Conclusion

For the foregoing reasons it is submitted that the Office cannot maintain a *prima facie* case of obviousness as required under 35 U.S.C. § 103(a). It is therefore respectfully requested that the rejection of claims 19, 23, 26 and 27 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Entry of a Notice of Allowance is solicited. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

/michele l lawson/

By:_____

Dated: February 12, 2010

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CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

I HEREBY CERTIFY that this correspondence is being electronically transmitted to the Patent and Trademark Office through EFS Web on February 12, 2010.

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Lauren Reeves